Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial

Eggermont, A M M ; Suciu, S ; Santinami, M ; Testori, A ; Kruit, W H J ; Marsden, J ; Punt, C J A ; Salès, F ; Gore, M ; Mackie, R ; Kusic, Z ; Dummer, R ; Hauschild, A ; Musat, E ; Spatz, A ; Keilholz, U

Abstract: BACKGROUND: Any benefit of adjuvant interferon alfa-2b for melanoma could depend on dose and duration of treatment. Our aim was to determine whether pegylated interferon alfa-2b can facilitate prolonged exposure while maintaining tolerability. METHODS: 1256 patients with resected stage III melanoma were randomly assigned to observation (n=629) or pegylated interferon alfa-2b (n=627) 6 mug/kg per week for 8 weeks (induction) then 3 mug/kg per week (maintenance) for an intended duration of 5 years. Randomisation was stratified for microscopic (N1) versus macroscopic (N2) nodal involvement, number of positive nodes, ulceration and tumour thickness, sex, and centre. Randomisation was done with a minimisation technique. The primary endpoint was recurrence-free survival. Analyses were done by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00006249. FINDINGS: All randomised patients were included in the primary efficacy analysis. 608 patients in the interferon group and 613 patients in the observation group were included in safety analyses. The median length of treatment with pegylated interferon alfa-2b was 12 (IQR 3.8-33.4) months. At 3.8 (3.2-4.2) years median follow-up, 328 recurrence events had occurred in the interferon group compared with 368 in the observation group (hazard ratio 0.82, 95% CI 0.71-0.96; p=0.01); the 4-year rate of recurrence-free survival was 45.6% (SE 2.2) in the interferon group and 38.9% (2.2) in the observation group. There was no difference in overall survival between the groups. Grade 3 adverse events occurred in 246 (40%) patients in the interferon group and 60 (10%) in the observation group; grade 4 adverse events occurred in 32 (5%) patients in the interferon group and 14 (2%) in the observation group. In the interferon group, the most common grade 3 or 4 adverse events were fatigue (97 patients, 16%), hepatotoxicity (66, 11%), and depression (39, 6%). Treatment with pegylated interferon alfa-2b was discontinued because of toxicity in 191 (31%) patients. INTERPRETATION: Adjuvant pegylated interferon alfa-2b for stage III melanoma has a significant, sustained effect on recurrence-free survival.

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Adjuvant Therapy With Pegylated Interferon α-2b Versus Observation in Resected Stage III Melanoma: Final Results of EORTC 18991, a Randomised Phase 3 Trial

Alexander MM Eggermont, Stefan Suciu, Mario Santinami, Alessandro Testori, Wim HJ Kruit, Jeremy Marsden, Cornelis JA Punt, François Salès, Martin Gore, Rona MacKie, Zvonko Kusic, Reinhard Dummer, Axel Hauschild, Elena Musat, Alain Spatz, Ulrich Keilholz

- *Other members of the EORTC Melanoma Group are listed on Appendix 1*

Erasmus University Medical Center, Rotterdam (Prof A.M.M. Eggermont, MD, PhD and W.H.J. Kruit, MD, PhD); **EORTC Headquarters, Brussels** (S. Suciu, MSc, PhD and E. Musat, MD); **Istituto Nazionale dei Tumori Milan** (M. Santinami, MD); **Istituto Europeo di Oncologia, Milan** (A. Testori, MD); **University Hospital Birmingham, Birmingham** (J. Marsden, MD); **University Nijmegen Medical Center – St Radboud , Nijmegen** (Prof C.J.A. Punt, MD, PhD); **Institut Jules Bordet, Brussels** (F. Salès, MD**)**; **Royal Marsden Hospital NHS, London** (Prof. M. Gore, MD); **University of Glasgow** (Prof. R. MacKie, MD, DSc); **University Hospital Sestre Milosrdnice, Zagreb** (Prof Z. Kusic, MD); **University Clinic Zürich (**Prof. R. Dummer, MD); **University Hospital Kiel, Kiel** (Prof. A. Hauschild); **Institut Gustave-Roussy, Villejuif** (A. Spatz, MD); **Charité-Benjamin Franklin Campus, Berlin** (Prof U. Keilholz, MD, PhD)

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Corresponding author
Alexander M.M. Eggermont, MD, PhD
Professor and Head Surgical Oncology
Erasmus University Medical Center – Daniel den Hoed Cancer Center
301 Groene Hilledijk
3075 EA Rotterdam, the Netherlands
Email: a.m.m.eggermont@erasmusmc.nl

Summary

Background Any benefit of adjuvant interferon α-2b (IFNα-2b) for melanoma may depend on dose and duration of treatment. Pegylated interferon α-2b (PEG-IFNα-2b) may facilitate prolonged exposure while maintaining tolerability.

Methods 1256 patients with resected Stage III melanoma were randomised to receive observation or PEG-IFNα-2b induction 6 µg/kg/wk for 8 weeks then maintenance 3 µg/kg/wk for an intended duration of 5 years. Randomization was stratified for microscopic (N1) vs macroscopic (N2) nodal involvement, number of positive nodes, ulceration and tumour thickness. Recurrence-free survival (RFS) (primary endpoint), distant-metastasis-free survival (DMFS), and overall survival (OS) were analyzed for the intent-to-treat population.

Results At 3.8 years median follow-up, RFS was reduced by 18% (hazard rate [HR] 0.82; *P*=0.01) in the PEG-IFNα-2b arm compared with observation; the 4-year RFS rate was 45.6% vs 38.9%. DMFS was improved, but non-significantly (P=0.11). OS was unchanged. In stage III-N1, both RFS (HR 0.72, 57.7% vs 45.4%, P=0.01) and DMFS (HR 0.73, 60.5% vs 52.6%, P=0.01) were prolonged in the PEG-IFNα-2b arm, whereas in stage III-N2 there was no benefit. Grade 3 and 4 adverse events occurred in 38% and 9% in the PEG-IFNα-2b arm and 9% and 7% in the observation arm. PEG-IFNα-2b was discontinued in 31% because of fatigue (15%), depression (6%), hepatotoxicity (10%).

Interpretation Adjuvant PEG-IFNα-2b for stage III melanoma had a significant sustained impact on RFS. For N1 disease the impact was also significant for DMFS. Patients with lower disease burden clearly benefited more, consistent with our previous trial EORTC 18952 of IFNα-2b.

Keywords: Pegylated interferon α-2b; interferon α-2b; melanoma; high-risk; recurrence; EORTC

Trial registration information:

Clinicaltrials.gov

NCT number (NCT00006249). ·

http://clinicaltrials.gov/ct/show/NCT00006249?order=1

Introduction

Interferon (IFN)α-2b is the most investigated agent for adjuvant treatment of patients with stage IIb (primary tumor ≥ 4 mm, node-negative) and stage III (any primary tumor, node-positive) melanoma, both groups at high risk of recurrence after definitive surgery.(1) Results from multiple controlled trials suggest that the role of an induction period, the optimum dose and duration for adjuvant interferon α in high-risk melanoma remain to be defined.(2;3) Individual trials of high- and intermediate-dose interferon α-2b for patients at high risk of melanoma recurrence after resection have been shown to improve recurrence-free survival (RFS) without, however, showing consistent effects on overall survival (OS) compared with observation alone.(4;5;6;7) Low- and intermediate-dose regimens with either IFNα-2b or IFNα-2a, while more tolerable for longer periods of time, have produced transient improvements in RFS or DMFS, again without a significant impact on OS.(7;8;9;10;11) A recent meta-analysis of 13 randomised trials estimated the benefit of interferon α for reducing the risk of recurrence or death at 13% for RFS (P<0.0001) and the risk of death at 10% for OS (P=0.008), without, however, defining the optimum dose or duration of interferon therapy.(12).

An important contribution to the design of EORTC 18991, was provided by the outcome of EORTC trial 18952 trial regarding the differential effects of dose and duration of IFN therapy in high-risk melanoma. In trial 18952, 1388 patients were randomised to receive a 4-week induction period of 10 million units (MIU) IFN 5 days/week followed by either 10 million units (MIU) three times weekly for 12 months (intermediate higher dose) or 5 MIU three times weekly for 24 months (intermediate lower dose), or observation.. The lower-dose 25-month regimen resulted in a 19% risk reduction for distant metastasis-free

interval (DMFI) (*P*=0.029, borderline significant), while the intermediate-dose, 13-month regimen had no effect on DMFI, suggesting longer duration of treatment with lower doses may be more effective than shorter-term therapy at higher doses.(7)

By enabling prolonged, weekly self-administered adjuvant therapy, pegylated interferon α-2b (PEG-IFNα-2b) has the potential to improve the benefit-toxicity balance for patients with resected stage III melanoma. Therapy with PEG-IFNα-2b has been shown to maintain maximal exposure to interferon α-2b for 48 to 72 hours, with a measurable residual trough level, compared with rapid decline from peak plasma concentrations for unpegylated IFNα-2b in patients with chronic hepatitis C, allowing once-weekly rather than three-times weekly subcutaneous (sc) injections.(13)

EORTC 18991 clinical trial here reported is a randomised phase 3 controlled study of adjuvant therapy conducted in stage III melanoma, where the efficacy and toxicity of PEG-IFNα-2b were compared with observation. The rationale was to provide a self-administered treatment with prolonged exposure, for maximum of 5 years. The study was designed to allow dose reductions to maintain ECOG performance status at a score of 0 to 1 throughout the course of treatment.

The study of 1256 patients, was designed to measure an improvement in distant metastasis-free survival (DMFS) so that treatment could be continued in the event of local or regional relapse. In prior consultation with the European regulatory authorities and at the request of the United States Food and Drug Administration, the endpoint was revised prior to trial analysis to relapse-free survival (RFS), defined as the length of time from randomisation to the first of local regional or distant recurrence of melanoma or death of any cause. Secondary endpoints of the study included DMFS, overall survival

(OS), and safety. The results reported here are the final analysis, and the planned 10-year survival follow-up is ongoing.

Patients

Patients 18 to 70 years of age with histologically documented stage III melanoma (TxN1-2M0) were enrolled.(1) The primary cutaneous melanoma must have been completely excised with adequate surgical margins and complete regional lymphadenectomy must have occurred 70 days or less before randomisation. Patients were required to have adequate hepatic, renal, and bone marrow function before enrollment. Exclusion criteria for this study included ocular or mucous membrane melanoma, evidence of distant metastasis or in-transit metastasis, prior malignancy within the past 5 years (other than surgically resected non-melanoma skin cancer or cervical carcinoma in situ), autoimmune disease, uncontrolled infections, cardiovascular disease, liver or renal disease, use of systemic corticosteroids, and prior systemic therapy for melanoma. All patients provided written informed consent before randomisation. The following criteria to defined disease sub-stage were used: only microscopic, non-palpable nodal involvement (including those staged with sentinel node biopsy) or clinically palpable nodal involvement (synchronous with removal of the primary tumor or discovered after prior removal of the primary tumor). The protocol was approved by the EORTC protocol review committee and the local institutional ethical committees.

Study design

Patients were randomly assigned in a 1:1 ratio to one of 2 groups: pegylated interferon α-2b treatment for 5 years or observation. Randomisation was performed centrally at the EORTC Data Center using minimization techniques.(14;15) Patients were stratified by disease substage (N1:microscopic vs N2:clinically palpable lymph nodes), number of involved lymph nodes, Breslow thickness of the primary tumor, ulceration of the primary tumor (present vs absent vs unknown), sex and center. N1 patients, were almost exclusively sentinel node (SN) – positive patients.

Pegylated interferon α-2b was administered at 6 µg/kg/wk subcutaneously (sc) for 8 weeks (induction), followed by 3 µg/kg/wk sc (maintenance) for an intended treatment duration of 5 years. Stepwise dose adjustments (6 µg/kg/wk to 3, 2, and 1 µg/kg/wk during the induction phase and from 3 µg/kg/wk to 2 and 1 µg/kg/wk during the maintenance phase) of pegylated interferon α-2b were specified by the study protocol to adjust for toxicity and in order to maintain an ECOG performance status of 0 or 1 for each patient. Treatments could be interrupted for surgery for local or regional recurrence of melanoma, then resumed after surgery.

Efficacy evaluation

Patients in both arms of the study were evaluated for recurrence and distant metastases every 3 months during the first 3 years and every 6 months thereafter. Physical examination, chest radiography, computed tomography, and other imaging techniques were employed as clinically indicated. Recurrence or metastatic lesions were confirmed pathologically. The primary endpoint of the study was recurrence-free survival (RFS),

defined as time from randomisation to any local or regional recurrence, distant metastasis, or death for any reason. Secondary endpoints included distant metastasis-free survival (DMFS), defined as time from randomisation to any distant metastasis or death for any reason, and overall survival (OS), defined as time from randomisation to death. An Independent Review Committee used a blinded review process to determine the dates of events and censoring from individual patient data (= last date of disease evaluation for RFS and DMFS). These dates form the basis of the primary analysis.

Toxicity evaluation

The occurrence of adverse events was evaluated at each follow-up visit by physical examination, specific questioning of the patient, and by spontaneous reports. All reported adverse events were graded according to the Common Toxicity Criteria version 2·0.(16) Hematological and laboratory parameters were evaluated at each visit and also as clinically indicated.

Statistical analysis

The sample size was calculated to be at least 1200 patients in order to observe approximately 576 distant metastases or deaths. With 576 events the study would have approximately 90% power to detect a hazard ratio of 0.76 for DMFS, or a 9.75% difference (from 40% to 49.75%) at 4 years.(17) Actuarial curves for RFS, DMFS and OS were calculated with the Kaplan-Meier technique and the standard errors (SE) of the estimated rates at 4 years from randomisation were obtained via the Greenwood

formula.(18) The Cox proportional hazards model was used to obtain the hazard ratio for the treatment comparison - event rate in the PEG-IFNα-2b group versus the event rate in the observation group - and its 95% confidence interval (CI), adjusted for all factors used at randomisation. For subgroup analyses, the treatment comparison was considered to be significant at the 1% level, and therefore, the 99% CI of the hazard ratio was computed. All efficacy analyses were based on the intent-to-treat population, whereas for toxicity analysis only patients who started the treatment/observation allocated by randomisation and were documented regarding adverse events were included.

The cut-off date was 31st of March 2006. The database, located at the EORTC Data Center, was frozen in December 2006 and SAS 9.1 software (SAS Institute Inc, Cary, NC, USA) has been used for the statistical analyses.

Results

Between October 2000 and August 2003, 1256 patients were randomised from 99 institutions in 17 countries, mainly in Europe. There were 627 patients in the PEG-IFNα-2b arm and 629 patients in the observation arm (see **Appendixes 1 and 2**).

Patient characteristics

The median age of the study population was 50 years, with 11% of patients over 65 years (**Table 1**). Demographics and baseline characteristics were very well balanced across both treatment arms. Approximately 40% of patients had microscopic nodal disease and

60% had clinically palpable nodal disease. The ECOG performance status was 0 in 84% of patients and 1 in 16%.

Treatment feasibility and inclusion in analyses according to CONSORT statement

Out of 1256 patients, 23 (1.4%) were considered ineligible (9 in PEG-IFNα-2b and 14 in observation): 6 due to delays of over 70 days between surgery and randomisation, 6 because of incorrect staging, 1 because of additional malignancy, 1 with unacceptable concomitant treatment, 4 with abnormal laboratory values, and 5 for other reasons.

Figure 1 shows the treatment allocation and follow up details by treatment arm.

The median overall treatment duration was 8 weeks for induction and 15 months for maintenance. At 12 months after randomisation, 311 (50%) subjects randomised to treatment were under PEG-IFNα-2b treatment. At 4 years, approximately 22% of patients remained in the treatment arm of the study vs 38% in the observation arm.

Efficacy

Overall treatment results and comparisons

After a median 3.8 years of follow-up, a total of 696 recurrences or deaths had occurred: 328 in PEG-IFNα-2b and 368 in observation arm (**Table 2**). Patients allocated to PEG-IFNα-2b had their risk of recurrence or death significantly reduced by 18% (hazard ratio 0.82, 95% confidence interval (CI) 0·71–0·96) as compared with those randomised to observation (P=0.01). There was a 6.7% (95% CI 0.6%-12.8%) absolute difference in the estimated 4-year rates of RFS: 45.6% in the PEG-IFNα-2b group vs 38.9% in the

observation group. Kaplan-Meier analysis showed that the benefit of treatment began early and was consistent throughout the study (**Figure 2 A**).

Multivariate analysis indicated that treatment comparison adjusted for all stratification factors used at randomisation remained significant (P=0.02): hazard ratio 0.84, 95% CI (0.73-0.98).

Results for DMFS in the whole population were consistent with those for RFS without reaching statistical significance (**Table 2** and **Figure 2B**). The difference in the median time to DMFS was similar to that observed for RFS, at 9 months (44 months in the PEG-IFNα-2b arm and 36 months in the observation arm). A total of 629 distant metastases or deaths occurred: 304 vs 325. There was a 2.8% difference in the 4-year DMFS rates: estimated 4-year rates of DMFS were 48.2% and 45.4% for the treatment and observation arms, respectively.

Overall survival was not significantly different (P=0.78) between the 2 treatment groups: the estimated 4-year overall survival rate was 56.8% in the PEG-IFNα-2b arm and 55.7% in the observation arm (**Table 2** and **Figure 2C**).

Subgroup analysis

The benefits of treatment with PEG-IFNα-2b are more pronounced in patients with earlier Stage III melanoma disease than in those with later stage disease (**Table 3** and **Figure 3**). In patients with microscopic nodal disease (N1), a reduction of 27% in the risk of recurrence or death (RFS hazard ratio 0.73, 99% CI 0.53–1.02; P=0.016) was observed in the PEG-IFNα-2b arm compared with observation and an improvement of 12.3% (99% CI -2.6%-27.2%) in the 4-year RFS. Similarly, the risk of distant metastases or death was

reduced by 25% (DMFS hazard ratio 0.75, 99% CI 0.52–1.07; *P*=0.03) and the 4-year DMFS rate was improved by 7.9%. The treatment difference in OS is, to date, not significant (P=0.43). These results were confirmed by multivariate analyses. In contrast, patients with palpable nodal disease (N2) showed non significant or no improvement for RFS, DMFS, and OS respectively (**Table 3** and **Figure 4**).

Similarly patients with tumor involvement limited to one lymph node achieved reductions in the risk of recurrence or death with PEG-IFNα-2b treatment (hazard rate 0.71 99% CI 0.71–0.97; P=0.004), as well as reductions in the risk of distant metastases or death (hazard rate 0.73, 99% CI 0.53–1.00; P=0.01), and even in the risk of death (hazard ratio 0.83, 99% CI 0.58-1.19), compared with patients with more than one involved lymph nodes, for whom such reductions were more limited or not seen at all. Kaplan-Meier curves patients with one lymph node involvement showed that the benefit of treatment with pegylated interferon α-2b began quite early in the study and was maintained throughout the study. The 4-year rate treatment benefit was 11.2% (99% CI 0.4%-22.0%), 9.5% and 5.8% regarding RFS, DMFS and OS respectively (**Table 4**).

In patients with lowest tumor burden (*microscopic nodal involvement of only one node*), 194 (PEG-IFNα-2b) vs 188 (observation), the treatment difference was significant for RFS (hazard ratio 0.64, 99% CI 0.42-0.98; P=0.006) and DMFS (hazard ratio 0.63, 99% CI 0.40-1.00; P=0.009), but not for OS (hazard ratio 0.76, 99% CI 0.44-1.30; p=0.18). The estimated improvement in 4-year rates was 14.6% (99% CI -0.1%-29.3%), 11.7% and 7.3% respectively for these 3 endpoints (**Table 5**).

In the subgroup of patients with *any number of microscopic nodal involvement and who had an ulceration in the primary tumor* the impact of PEG-IFNα-2b was significant or

almost significant for the 3 endpoints: for RFS (hazard ratio 0.69, 99% CI 0.43-1.12; P=0.05), DMFS (hazard ratio 0.59, 99% CI 0.35-0.98; P=0.006) and OS (hazard ratio 0.61, 99% CI 0.34-1.10; P=0.03) (**Table 5**). This was not the case in those with microscopic nodal involvement and who had non-ulcerated primary (data not shown).

Toxicity and cause of death: treatment comparison

Adverse events of any severity that were recorded in more than 4% of patients in the PEG-IFNα-2b and observation arms are shown in **Table 6.** NCI-CTC grade 3 events occurred in 239 (38%) of patients in the PEG-IFNα-2b arm and in 58 (9%) of patients in the observation arm. Grade 4 events occurred in 58 (9%) of patients in the PEG-IFNα-2b arm and in 42 (7%) of patients in the observation arm. A total of 191 (31%) patients in the PEG-IFNα-2b group discontinued treatment due to toxicity. Adverse events most frequently associated with drug discontinuation included fatigue (25%), depression (16%), anorexia (14%), nausea (12%), liver function tests (12%), and pyrexia (10%).

A total of 525 deaths were reported; 262 in the PEG-IFNα-2b arm and 263 in the observation arm. The incidence of the most frequent cause of death, malignant disease, was similar in the 2 arms: 249 of 627 (42%) in the pegylated interferon α-2b arm and 244 of 629 (42%) in the observation arm. Cardiovascular disease was the main cause of death for 5 patients (1 patient without previous relapse) in the treatment arm and 3 patients in the observation arm and infection was the cause of death for 1 patient in each arm. Other causes of death were rare and equally distributed between the 2 arms of the study.

Discussion

A major strength of this EORTC 18991 trial is that, with 1256 patients entered, it is the largest Phase 3 study of adjuvant therapy in stage III melanoma to date, that it was stratified for biologically important factors such as microscopic low tumor burden vs macroscopic high tumour burden, and for ulcerated primaries vs non-ulcerated primaries and that it shows a sustained, clinically relevant, statistically significant benefit in PEG-IFNα-2b treated patients. At 3·8 years median follow-up, it shows an increase in median RFS of 9.2 months and an absolute increase in estimated 4-year RFS rate from 38.9% in the observation arm to 45.6% in the PEG-IFNα-2b arm. This 6.7% improvement in 4-year RFS indicates that these results are consistent with an increase of the long-term RFS rate for 1 in approximately every 15 patients with high risk cutaneous melanoma if they receive adjuvant treatment with PEG-IFNα-2b instead of observation only.

In addition, analysis of secondary endpoints are supportive, showing encouraging but non-significant increases in DMFS. The toxicity profile of PEG-IFNα-2b is acceptable over a maximum 5-year duration of treatment. Side effects of interferon α-2b most often encountered include fatigue and depression. They are higher early in treatment and do not increase as treatment progresses. Patients also attribute less percentage of time to these effects as treatment progresses.

These results also show that the Peg-IFN effect is sustained throughout the 5-year treatment period. Our results are also consistent with results from EORTC 18952 of adjuvant interferon α-2b in stage IIb and III melanoma.(7) In 18952 subgroups of patients with earlier stage disease and/or lower disease burden also experienced a more pronounced treatment effect, with greater risk reductions and longer durations of RFS

and DMFS. Survival, though as yet immature, appears to trend consistently with RFS and DMFS. The subgroup of patients with microscopic nodal involvement represented approximately 40% of the our study population, and observation of microscopic nodal involvement in stage III disease can be expected to increase significantly, due to widespread use of SN biopsy.(19) The safety of this regimen appeared very acceptable and favourable compared to that reported over consecutive earlier trials for high-dose IFNα-2b which report grade 3-4 fatigue incidence of up to 24%, depression of 10% and liver toxicity 29%.(5) By contrast, EORTC 18991 patients report a rate of fatigue grade 3-4 limited to 15% (grade 4 <1 %), depression grade 3 of 6% (grade 4(<1%)) and liver toxicity grade 3 of 10% (grade 4: <1%). Finally, unlike high-dose IFNα-2b the toxicity does not tend to increase with increased duration of treatment.

The data from EORTC study 18991 establishes PEG-IFNα-2b as an option for adjuvant treatment of patients with resected high-risk melanoma, especially those with lower nodal tumor burden. The aim of adjuvant therapy for high-risk melanoma, as for other major cancers, is to provide a tolerable treatment that reduces the risk of relapse for many patients and potentially achieves a cure. In our study, as an absolute difference of 12.3% in the 4-year RFS was observed, in patients with microscopic nodal disease in resected stage III melanoma, PEG-IFNα-2b treatment could be considered in this subgroup, since the observation of IFN-mediated efficacy in early stage III disease is fully consistent with observations in the EORTC 18952 trial, where stage III patients were also stratified by microscopic involvement vs palpable nodal involvement. Moreover these data are fully consistent with the impact observed in the French and the Austrian adjuvant trials with low dose IFN in non-SN-staged stage II melanoma patients, which showed a clear impact

on RFS and some effect on OS in trials where the events were most likely caused by the N1 (SN-positive) patient populations.(8;9) Less advanced disease (N1) may differ biologically from advanced disease (N2) and it seems to be more sensitive to the effects of IFN. Another observation made in the exploratory analyses of subgroups indicated that ulcerated primary melanomas seemed to more sensitive to IFN as non-ulcerated melanomas. This also points in the direction of biologic differences and needs to be explored further.

A further strength of trial 18991 is the decision to retain an observation only arm as the comparator with pegylated interferon. This is well illustrated by the problems arising from the recent observation of a detrimental effect of vaccine GM2 in EORTC trial 18961 on DMFS and OS leading to early cessation (at the 2nd interim analysis) of the trial. This development affects the recent meta analysis of current interferon trials. In this meta-analysis (12) the absolute improvement of OS rate was only 3% (95% CI 1%-5%) at 5 years, and was based on an analysis including the ECOG 1694 trial, which compared high dose IFNα-2b to GM2 vaccination which was stopped early (also at the 2nd interim analysis) because of a significant difference in favor of IFN α-2b regarding RFS as well as OS.(20) This large trial can no longer be part of the meta-analysis and the results of rerunning of the meta analysis should be done, by integrating the 18991 data as well. Such meta-analysis will allow to check the consistency of our findings in subgroups.

Markers of patients likely to respond to interferon are needed, and this trial 18991 indicates that the combination of low tumour volume and an ulcerated primaty may be such a marker. This observation requires confirmation, and also investigation to establish its biological basis. In EORTC 18991 we cannot confirm the observation of Gogas and

colleagues who reported that patients treated with adjuvant interferon who developed auto-antibodies against thyroglobulin, antinuclear factors or cardiolipin had a significantly better outcome than patients that did not develop these signs of autoimmunity.(21) Neither in this trial 18991 nor in the earlier 18952 did those who developed auto-antibodies during the course of the study have, subsequently, a lower risk of relapse.(22;23)

In conclusion the combination of results obtained in this trial 18991 and the earlier 18952 strongly suggest a beneficial effect of adjuvant interferon therapy for the subpopulation of stage III patients who have low tumour volume as evidenced by microscopic only nodal disease. Similarly, increased benefit is observed in patients with an ulcerated primary tumour. These observations will concentrate interferon administration where it is most needed and protect those unlikely to respond from unnecessary toxicity.

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Contributors: A.M.M. Eggermont, S. Suciu and R.M. MacKie prepared the manuscript with the help of the other co-authors. S. Suciu was the statistician, E. Musat the co-ordinating physician and A. Spatz the pathologist for this trial. A. Hauschild performed the blinded independent review. All other co-authors were the major contributors in patient accrual for the EORTC 18991 trial.

Conflict of Interest

Acted as a consultant to Schering Plough within the last 3 years: A. Eggermont and A. Hauschild.

APPENDIXES

APPENDIX 1: Full list of participants

Institut Jules Bordet, Brussels (F. Salès, MD)
Cliniques Universitaires St. Luc, Brussels (J-F Baurain, MD)
Hopital Universitaire Erasme, Brussels (P. Vereecke, MD)
U.Z. Gasthuisberg, Leuven (J. Thomas, MD)
Clinique Notre-Dame de Grace, Gosselies (V. Verschaeve, MD)
Hopital Saint-Louis, Paris (L. Ollivaud, MD)
C.H.R. de Besancon – Hopital Saint-Jacques, Besancon (Pr. F. Aubin, MD)
C.H.R. de Grenoble – La Tronche, Grenoble (M-T Leccia, MD)
Institut Gustave Roussy, Villejuif (MF. Avril, MD, C. Robert, MD)
Centre Leon Berard, Lyon (Pr. S. Negrier, MD)
Hopital St. Eloi, Montpellier (Pr. B. Guillot, MD, O. Dereure, MD)
Hospices Civils de Strasbourg, Strasbourg (D. Lipsker, MD)
Hopital St. Andre, Bordeaux (M. Delaunay, MD)
Centre Alexis Vautrin, Vandoeuvre-Les-Nancy (L. Geoffrois, MD)
Centre Rene Huguenin, Saint-Cloud (C. Vilmer-Renaud, MD)
C.H.R. de Lille, Lille (Pr. F. Piette, MD)
Centre Eugene Marquis, Rennes (T. Lesimple, MD)
C.H.R. Metz-Thionville, Thionville (F. Truchetet, MD)
CRLC Val d'Aurelle, Montpellier (D. Cupissol, MD)
C.H.U. de Bordeaux – Hopital Du Haut Leveque, Pessac (Pr. M. Beylot-Barry, MD)
C.H.R.U. De Limoges, Limoges (Pr. C. Bedane, MD)
Hopital De L'Archet, Nice (Pr. J-P Lacour, MD)
C.H.U. de Tours, Hopital Trousseau, Tours (L. Machet, MD)
C.H.U. de Saint-Etienne – Hopital Nord, Saint Etienne (Pr. F. Cambazar, MD, J. Perrot, MD)
C.H.U. Ambroise Pare, Boulogne-Billancourt (Pr. P. Saiag, MD)
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Vrije Universiteit Medisch Centrum, Amsterdam (A. Van Den Eertwegh, MD)
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David Maddison Clinical Sciences, Newcastle (Pr. P.Hersey, MD)
National Centre of Oncology, Sofia (K. Stoychkov, MD, Pr. Y. Stoychkov, MD)

Appendix 2

Total number of patients included per country

Country	Total
Australia	36
Belgium	68
Bulgaria	29
Croatia	31
Czech Republic	5
Estonia	5
France	106
Germany	103
Israel	8
Italy	229
Poland	28
Portugal	33
Slovenia	17
Spain	35
Switzerland	44
The Netherlands	152
United Kingdom	327
Total	**1256**

Table 1.

Demographic and baseline characteristics and stratification factors for randomisation* by treatment group

	PEG-IFNα-2b n=627 (100%)	Observation n=629 (100%)
Sex* (n, %)		
Female	261 (42)	262 (42)
Male	366 (58)	367 (58)
Age (years)		
Median (range)	50 (19–70)	50 (18–70)
18 to <50 (n, %)	311 (50)	311 (49)
50 to <65 (n, %)	252 (40)	238 (38)
≥ 65 (n, %)	64 (10)	80 (13)
Stage of disease* (n, %)		
Microscopic nodal disease	271 (43)	272 (43)
Clinically palpable nodes	356 (57)	357 (57)
No. Positive Lymph Nodes* (n, %)		
1	339 (54)	337 (54)
2–4	204 (33)	204 (32)
≥ 5	76 (12)	79 (13)
Not evaluable	8 (1)	9 (1)
Breslow thickness* (n, %)		
<1.5 mm	145 (23)	142 (23)
1.5 to 3.99 mm	267 (43)	270 (43)
≥ 4.0 mm	141 (22)	143 (23)
Unknown	74 (12)	74 (12)
Ulceration of primary* (n, %)		
No	302 (48)	304 (48)
Yes	156 (25)	156 (25)
Unknown	169 (27)	169 (27)
Ulceration of primary** (n, %)		
No	315 (50)	338 (54)
Yes	192 (31)	181 (29)
Unknown	120 (19)	110 (18)

**: indicated on case report forms (CRF)
Abbreviations: PegIFN α-2b, pegylated interferon α-2b

Table 2.

Treatment comparison - pegylated interferon α-2b (n=627) vs observation (n=629) - regarding several endpoints: recurrence-free survival (RFS), distant metastasis-free survival (DMFS), and overall survival (OS)

Results are expressed as estimates at 4 years (SE%), estimates of the hazard ratios (95% CI) and P-values

	RFS		**DMFS**		**OS**	
	PEG-IFN α-2b	Obs	PEG-IFN α-2b	Obs	PEG-IFN α-2b	Obs
No. of events	328	368	304	325	262	263
4-year rate (%) (SE %)*	45.6 (2.2)	38.9 (2.2)	48.2 (2.2)	45.4 (2.3)	56.8 (2.2)	55.7 (2.1)
Median* (months)	34.8	25.6	45.5	36.0	NR	NR
HR (95% CI)(**;1)	0.82 (0.71–0.96)		0.88 (0.75–1.03)		0.98 (0.82–1.16)	
P-value(**;1)	0.01		0.11		0.78	
HR (95% CI)(**;2)	0.84 (0.73-0.98)		0.90 (0.77-1.06)		1.00 (0.84-1.18)	
P-value(**;2)	0.02		0.20		0.98	
Treament x stage interaction***: P-value	0.34		0.18		0.48	

*: Kaplan-Meier estimates along with standard error (SE) obtained via the Greenwood formula

** P-value given by the Wald test (via a Cox model)

***: in a Cox model where treatment, stage and treatment x stage were included

(1): univariate analysis

(2): multivariate analysis (Cox model): treatment comparison adjusted for stage, number of lymph nodes involved, sex, ulceration, Breslow thickness, as indicated at randomization

Abbreviations: PegIFN α-2b, pegylated interferon α-2b; Obs, observation; NR, not reached; HR, hazard ratio; CI, confidence interval

Table 3.

Treatment comparison regarding recurrence-free survival (RFS), distant metastasis-free survival (DMFS) and overall survival (OS) according to stage III (microscopic vs palpable nodes) given at randomization

	RFS		**DMFS**		**OS**	
	PEG-IFN α-2b	Obs	PEG-IFN α-2b	Obs	PEG-IFN α-2b	Obs
Microscopic						
Nb. of events	108	137	93	117	73	81
4-year rates*	57.7 (3.3)	45.4 (3.5)	60.5 (3.6)	52.6 (3.5)	71.0 (3.0)	67.2 (3.2)
Median (mts)	NR	42.6	NR	55.4	NR	NR
HR (99%CI)(**;1)	0.73 (0.53-1.02)		0.75 (0.52-1.07)		0.88 (0.64-1.21)	
P-value(**;1)	0.016		0.03		0.43	
HR (99%CI)(**;2)	0.71 (0.51-1.00)		0.70 (0.49-1.00)		0.82 (0.54-1.25)	
P-value(**;2)	0.01		0.011		0.22	
Clinically palpable						
Nb. of events	220	231	211	208	189	182
4-year rates*	36.3 (2.8)	33.9 (2.6)	38.7 (2.8)	39.9 (2.7)	45.8 (2.8)	46.8 (2.8)
Median (yrs)	18.2	13.4	24	21.5	36	40.3
HR (99%CI)(**;1)	0.86 (0.68-1.10)		0.94 (0.73-1.21)		1.01 (0.83-1.24)	
P-value(**;1)	0.12		0.53		0.91	
HR (99%CI)(**;2)	0.88 (0.69-1.13)		0.97 (0.75-1.24)		1.04 (0.80-1.36)	
P-value(**;2)	0.18		0.72		0.70	

*: Kaplan-Meier estimates along with standard error (SE) obtained via the Greenwood formula
** P-value given by the Wald test (via a Cox model)
(1): univariate analysis
(2): multivariate analysis (Cox model): treatment comparison adjusted for number of positive lymph nodes, sex, ulceration, Breslow thickness, as indicated at randomization
Abbreviations: PegIFN α-2b, pegylated interferon α-2b; Obs, observation; NR, not reached; HR, hazard ratio; CI, confidence interval

Table 4:
Treatment comparison regarding recurrence-free survival (RFS), distant metastasis-free survival (DMFS) and overall survival (OS) according to number of positive lymph nodes given at randomization

	RFS		**DMFS**		**OS**	
	PEG-IFN α-2b	Obs	PEG-IFN α-2b	Obs	PEG-IFN α-2b	Obs
1 node						
Nb. of events	129	163	118	146	98	112
4-year rates*	59.6 (2.9)	48.4 (3.0)	62.4	52.9	69.4 (2.6)	63.6 (3.0)
Median (mts)	NR	44.4	NR	55.4	NR	NR
HR(99%CI)(**;1)	0.71 (0.53-0.97)		0.73 (0.53-1.00)		0.83 (0.58-1.19)	
P-value(**;1)	0.004		0.01		0.18	
HR(99%CI) (**;2)	0.69 (0.51-0.94)		0.70 (0.51-1.00)		0.82 (0.57-1.17)	
P-value(**;2)	0.002		0.005		0.15	
2-4 nodes						
Nb. of events	132	133	122	116	109	94
4-year rates*	32.8 (3.8)	33.0 (3.6)	35.9	41.7	44.9 (3.7)	52.3 (3.7)
Median (mts)	18.5	18.7	24	28.4	37.7	53.6
HR(99%CI)(**;1)	0.94 (0.69-1.29)		1.01 (0.73-1.42)		1.17 (0.81-1.68)	
P-value(**;1)	0.62		0.91		0.26	
5+ nodes						
Nb. of events	61	65	58	56	49	51
4-year rates*	18.6 (4.5)	15.7 (4.5)	20.3	26.0	34.8 (6.0)	33.0 (5.5)
Median (mts)	9.1	7.7	11.3	13.1	23.3	24.2
HR(99%CI)(**;1)	0.96 (0.61-1.53)		1.14 (0.71-1.85)		1.02 (0.61-1.70)	
P-value(**;1)	0.84		0.47		0.93	

*: Kaplan-Meier estimates along with standard error (SE) obtained via the Greenwood formula
** P-value given by the Wald test (via a Cox model)
(1): univariate analysis
(2): multivariate analysis (Cox model): treatment comparison adjusted for number of positive lymph nodes, sex, ulceration, Breslow thickness, as indicated at randomization

Abbreviations: PegIFN α-2b, pegylated interferon α-2b; Obs, observation; NR, not reached; HR, hazard ratio; CI, confidence interval

Table 5:
Treatment comparison regarding recurrence-free survival (RFS), distant metastasis-free survival (DMFS) and overall survival (OS).

Subgroup analysis in stage III-N1 (microscopic) patients with only 1 lymph node positive (LN+) or with an ulcerated primary melanoma (as indicated on CRFs)

	RFS		**DMFS**		**OS**	
	PEG-IFN α-2b	Obs	PEG-IFN α-2b	Obs	PEG-IFN α-2b	Obs
Nb. of LN+						
1						
Nb. pts/events	194/65	188/87	194/56	188/76	194/42	188/51
4-year (SE)*	63.8 (3.8)	49.2 (4.2)	66.7 (4.0)	55.0 (4.2)	76.7 (3.3)	69.4 (3.8)
Median (mts)	NR	47.2	NR	NR	NR	NR
HR(99%CI)(**;1)	0.64 (0.42-0.98)		0.63 (0.40-1.00)		0.76 (0.44-1.30)	
P-value(**;1)	0.006		0.009		0.18	
Ulceration						
Present						
Nb. pts/events	96/53	90/62	96/45	90/59	96/33	90/44
4-year rates*	43.8 (5.4)	26.8 (5.3)	47.4 (6.1)	30.1 (5.3)	65.0 (5.2)	45.4 (5.9)
Median (mts)	31.0	18.7	47.4	26.3	NR	42.2
HR(99%CI)(**;1)	0.69 (0.43-1.12)		0.59 (0.35-0.98)		0.61 (0.34-1.10)	
P-value(**;1)	0.05		0.006		0.03	

*: Kaplan-Meier estimates along with standard error (SE) obtained via the Greenwood formula
** P-value given by the Wald test (via a Cox model)
(1): univariate analysis

Abbreviations: PegIFN α-2b, pegylated interferon α-2b; Obs, observation; NR, not reached; HR, hazard ratio; CI, confidence interval

Table 6.

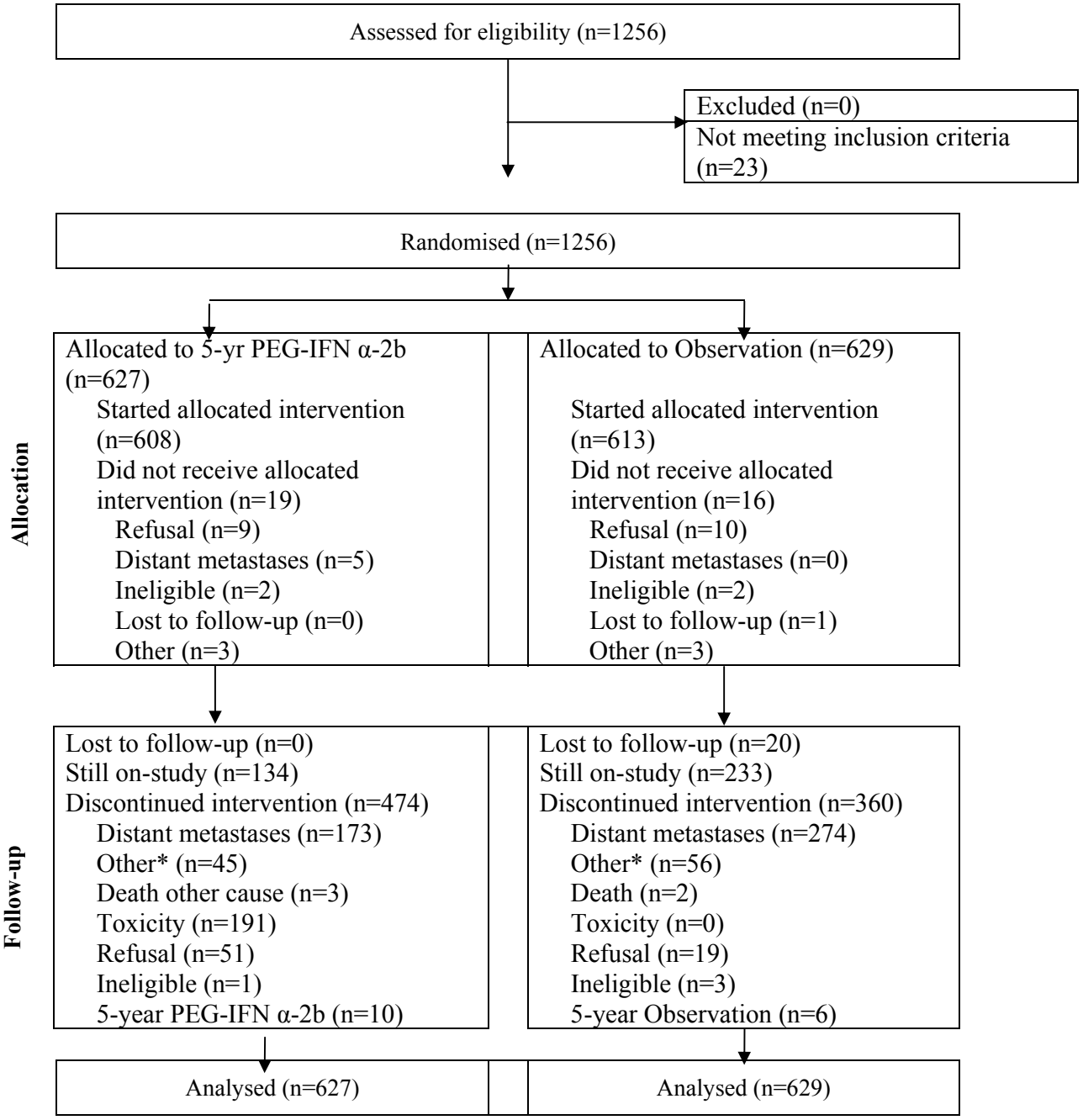
Adverse events (all, Grade 3, and Grade 4, in descending order of frequency) occurring in 4% or more (Grade 3 or 4 in the Pegylated interferon α-2b arm) of patients by treatment arm

n (%)	Pegylated interferon α-2b (n=613)			Observation (n=613)		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Any	608 (99)	239 (39)	58 (9)	492 (80)	58 (9)	42 (7)
Fatigue	574 (94)	89 (15)	8 (1)	252 (41)	7 (1)	0
Liver function test*	480 (78)	64 (10)	2 (<1)	221 (36)	8 (1)	2 (<1)
Pyrexia	454 (74)	24 (4)	1 (<1)	53 (9)	0	0
Headache	426 (69)	24 (4)	0	118 (19)	4 (1)	0
Myalgia	408 (67)	22 (4)	1 (<1)	140 (23)	3 (<1)	0
Depression	360 (59)	38 (6)	1 (<1)	153 (25)	2 (<1)	1 (<1)

*: SGOT/SGPT/Bilirubin/alkaline phosphatase

Figure 1.

Flow chart (cf CONSORT statement)



*: generally (± 50%) due to a loco-regional relapse

LEGEND OF FIGURES

Figure 2: Overall comparison

2A. Relapse-Free Survival according to randomised treatment arm.

N = Number of patients in each arm
O = Observed number of relapses (local, regional or distant metastasis) or deaths
P-value given by the logrank test

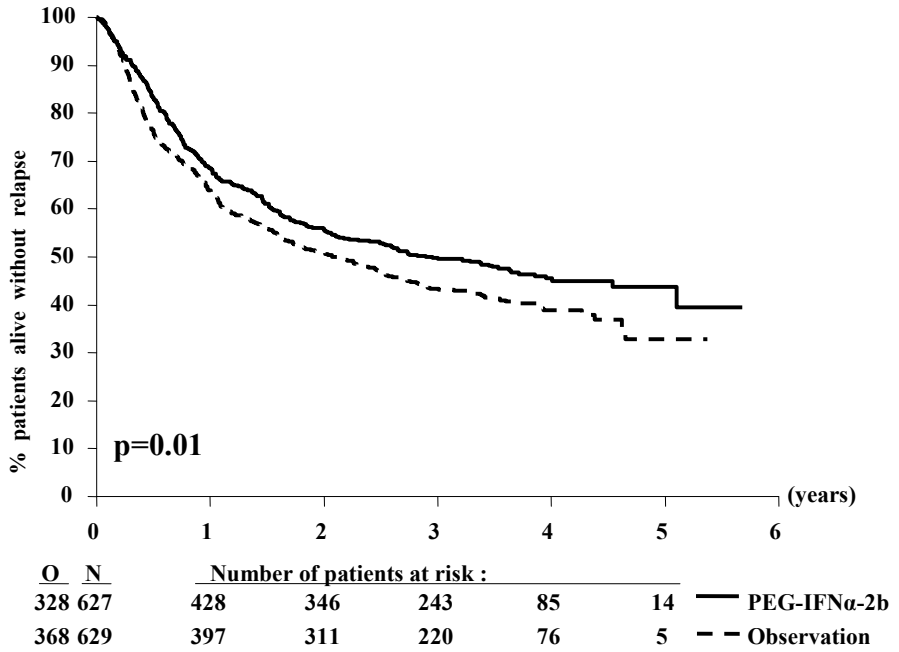
2B. Distant-Metastasis-Free Survival according to randomised treatment arm.

N = Number of patients in each arm
O = Observed number of distant metastasis or deaths
P-value given by the logrank test

2C. Duration of survival according to randomised treatment arm.

N = Number of patients in each arm
O = Observed number of deaths (whatever the cause)
P-value given by the logrank test

Figure 2A.



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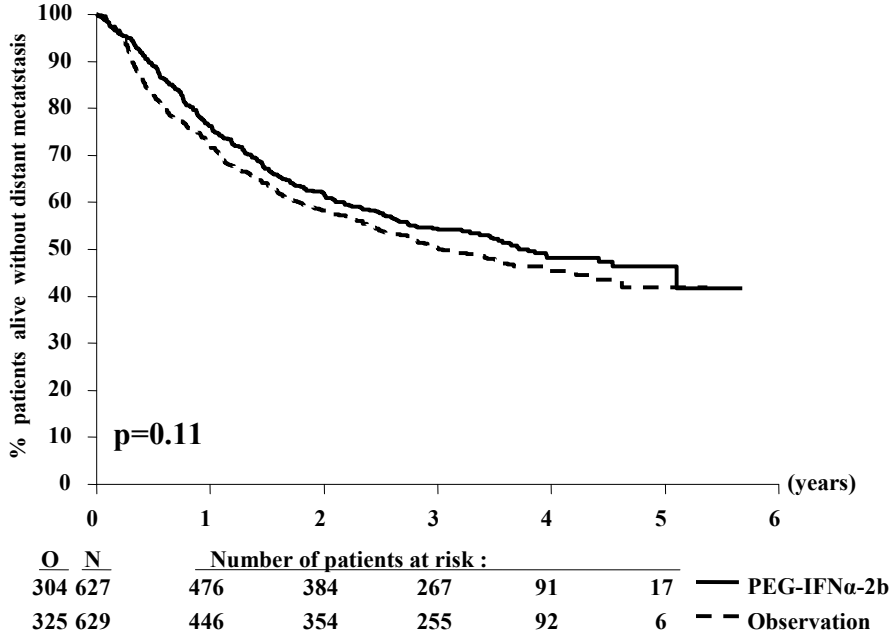


Figure 2C.

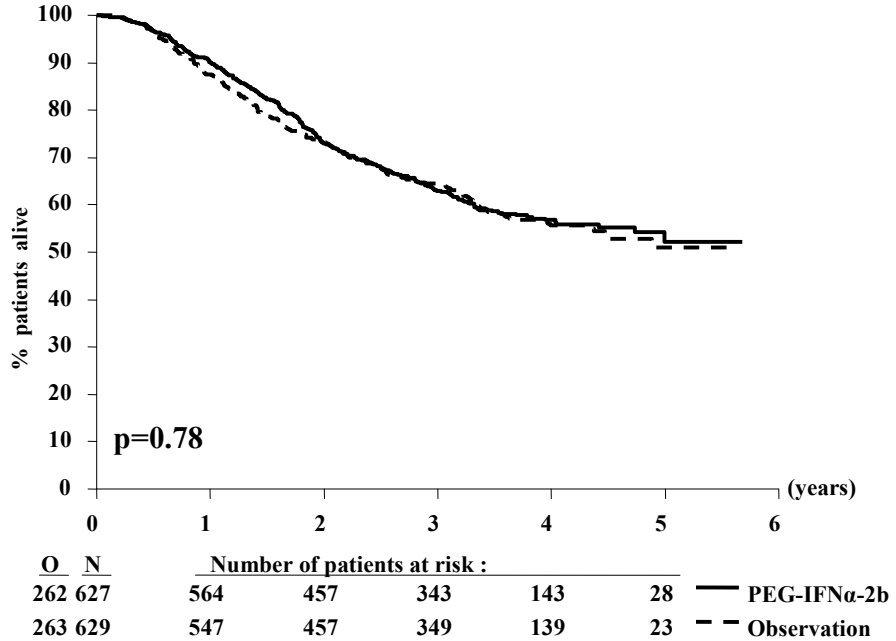


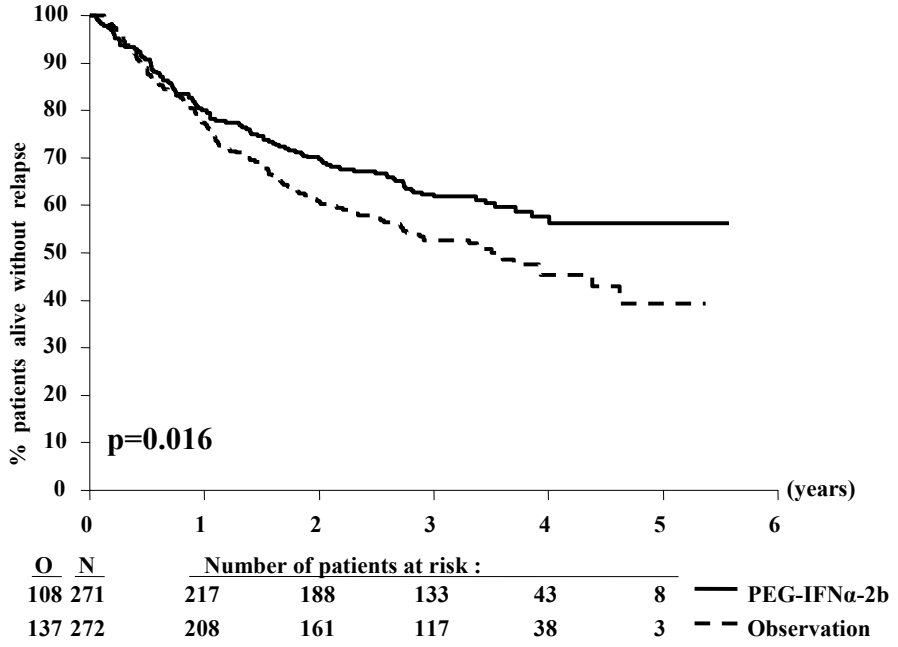
Figure 3: Stage III-N1 (microscopic nodal involvement only) patients

3A. Relapse-Free Survival according to randomised treatment arm.
N = Number of patients in each arm
O = Observed number of relapses (local, regional or distant metastasis) or deaths
P-value given by the logrank test

3B. Distant-Metastasis-Free Survival according to randomised treatment arm.
N = Number of patients in each arm
O = Observed number of distant metastasis or deaths
P-value given by the logrank test

3C. Duration of survival according to randomised treatment arm.
N = Number of patients in each arm
O = Observed number of deaths (whatever the cause)
P-value given by the logrank test

Figure 3A:



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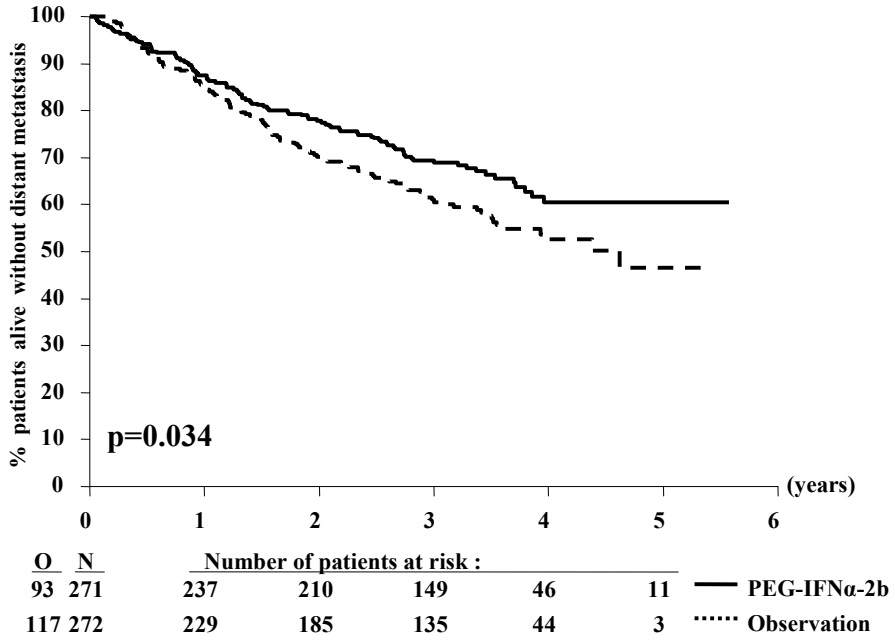


Figure 3C:

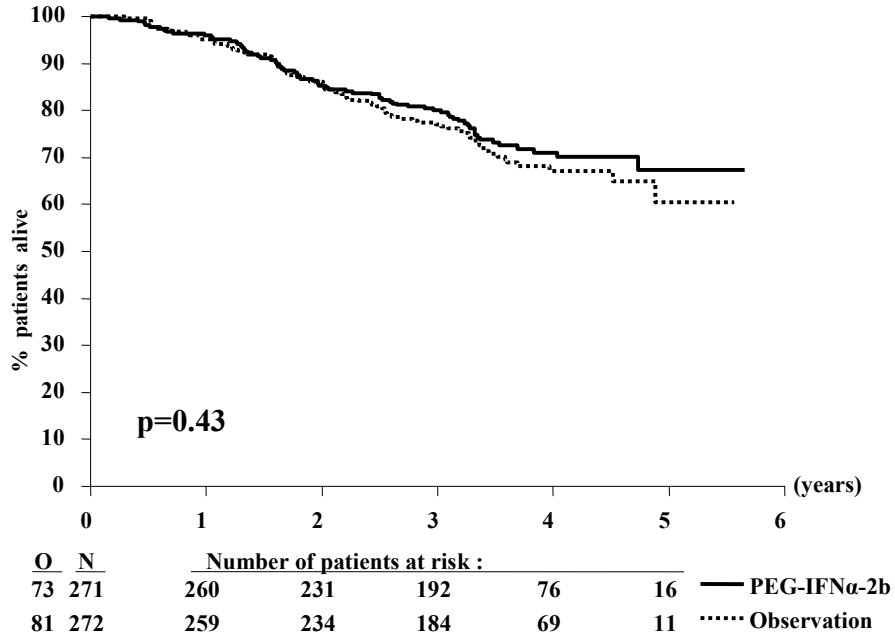


Figure 4: Stage III-N2 (palpable nodal involvement) patients

4A. Relapse-Free Survival according to randomised treatment arm.
N = Number of patients in each arm
O = Observed number of relapses (local, regional or distant metastasis) or deaths
P-value given by the logrank test

4B. Distant-Metastasis-Free Survival according to randomised treatment arm.
N = Number of patients in each arm
O = Observed number of distant metastasis or deaths
P-value given by the logrank test

4C. Duration of survival according to randomised treatment arm.
N = Number of patients in each arm
O = Observed number of deaths (whatever the cause)
P-value given by the logrank test

Figure 4A

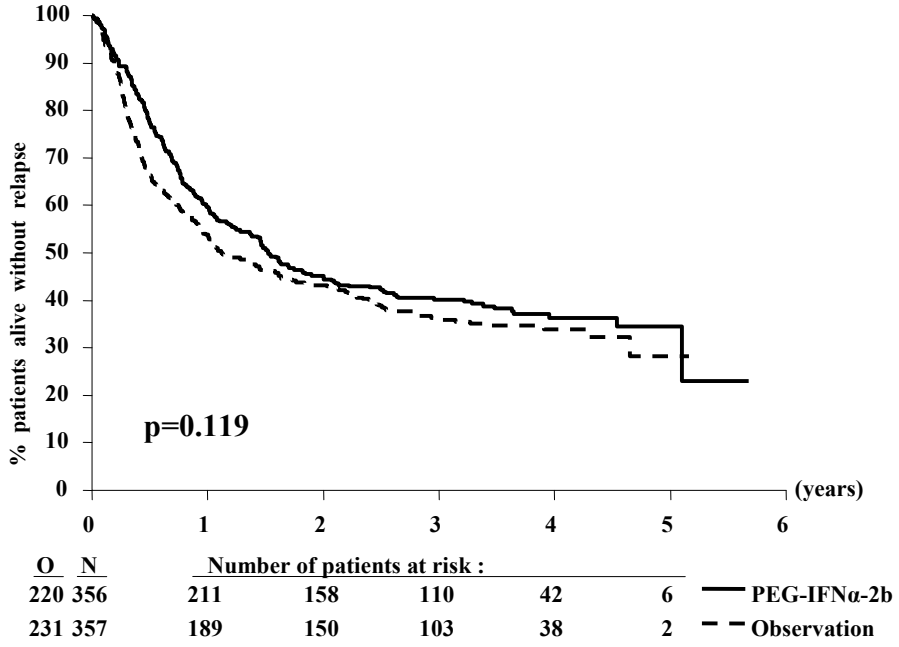


Figure 4B:

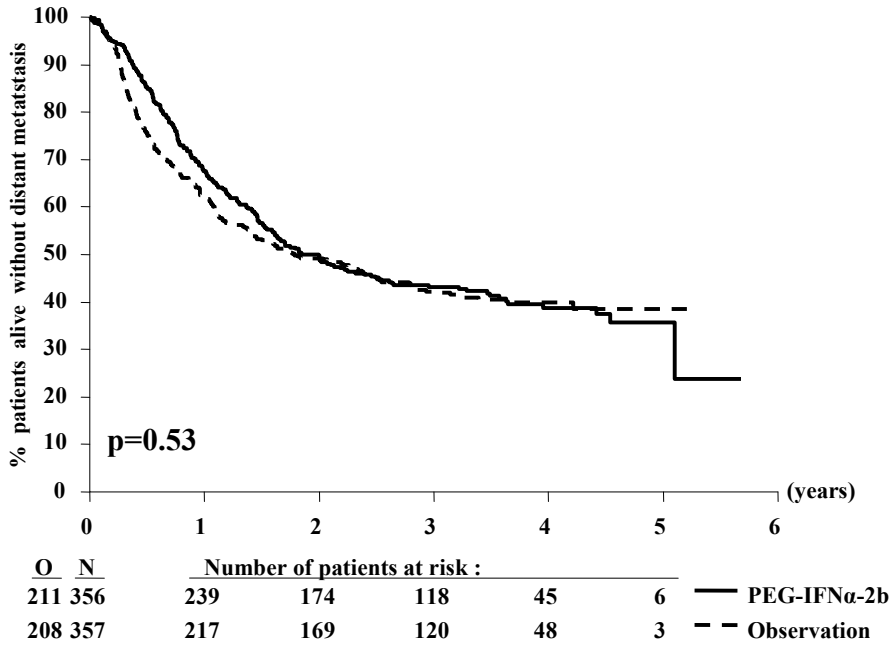
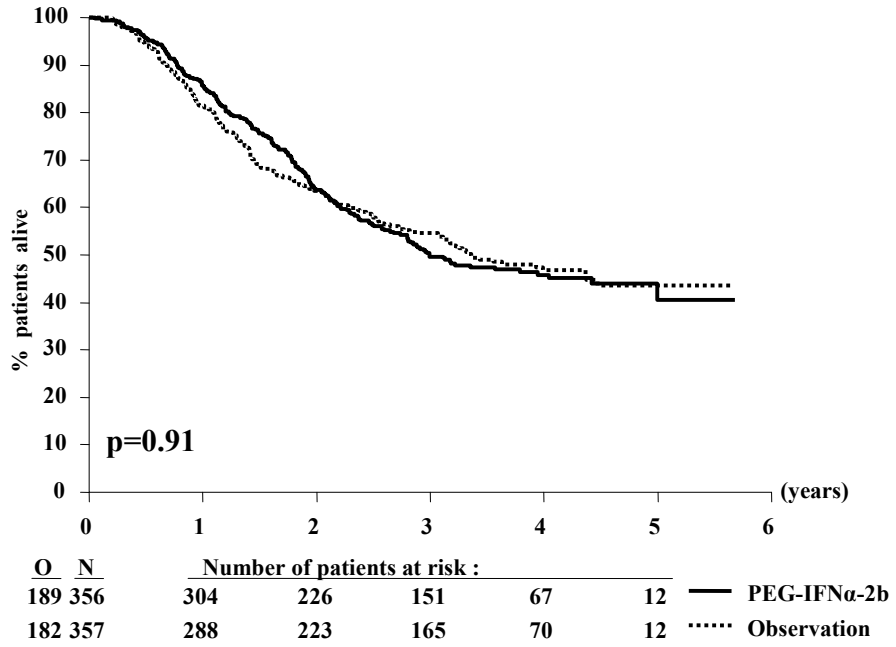


Figure 4C:



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